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(71) Applicant *(for all designated States except US)*: AKZO NOBEL N.V. [NL/NL]; Velperweg 76, P.O. Box 186, NL–6800 LS Arnhem (NL).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: GIVENS, Thomas, B. [US/US]; 3522 Red Mountain Road, Rougemont, NC 27572 (US). HUNLEY, Charles, W. [US/US]; 3601 South Point Drive, Apex, NC 27502 (US). FISCHER, Timothy, J. [US/US]; 4825 Winterwood Drive, Raleigh, NC 27613 (US). BOWLING, Regina, J. [US/US]; 1510 Pope Road, Creedmoor, NC 27522 (US).

(74) Agents: BLACKSTONE, William et al.; Akzo Nobel Patent Dept., 1300 Piccard Drive #206, Rockville, MD 20850 (US).

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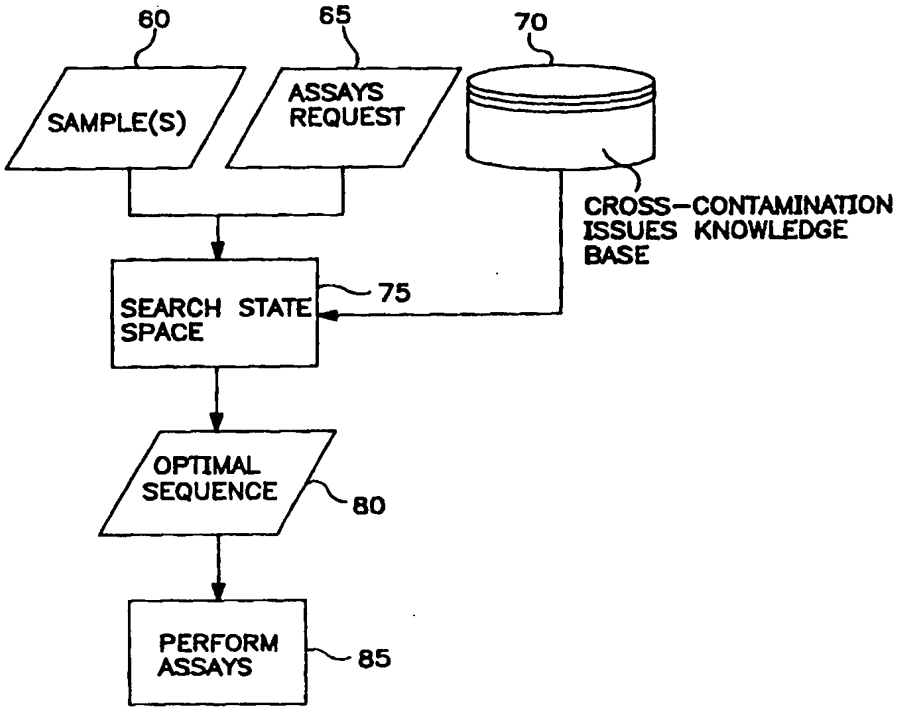
(54) Title: METHOD AND APPARATUS FOR OPTIMIZING ASSAY SEQUENCING ON A RANDOM ACCESS CLINICAL LABORATORY INSTRUMENT

(57) Abstract

A method and apparatus are disclosed for optimizing the sequence of assays on an automated random access instrument so as to reduce reagent cross–contamination problems. A common vehicle for reagent cross–contamination is the reagent probe surface which transfers reagents for the various tests. When a plurality of assays are run on a single sample, an initial best path (order of assays) is identified, after which the iterative process of looking for a better alternative begins. This process involves the application of a knowledge base concerning relationships associated with random access cross–contamination, to search the state space.



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METHOD AND APPARATUS FOR OPTIMIZING ASSAY SEQUENCING ON A RANDOM ACCESS CLINICAL LABORATORY INSTRUMENT

BACKGROUND OF THE INVENTION

This invention relates to the field of clinical laboratory medicine and specifically to assay sequencing on an automated random access clinical laboratory instrument. The invention is described in relation to the "MDA 180", an automated coagulation instrument from Organon Teknika, Durham, NC. Further features of such an automated coagulation instrument, beyond those set forth in the present application, can be found in U.S. patent application 08/389,986 to Fischer et al., the subject matter of which is incorporated herein by reference. However, the present invention is applicable to any automated or semi-automated random access clinical laboratory instrument that must contain cross-contamination from one assay to the next.

A major challenge with the automation of clinical analysis has been random access. Random access is the ability of an automated analyzer to run any subset of a variety of assays on a sample before the next sample is processed. The alternative to random access mode operation is batch mode, where each assay is performed on all available samples before processing the next assay. Random access can be difficult to implement when small amounts of reagents from one assay can affect the results of subsequent assays if allowed to carry over, causing "cross-contamination". The specimen for coagulation assays is blood plasma, a highly complex and sensitive biological material, and assay reagents frequently include enzymes or other bioactive molecules that affect coagulation results when present in minute amounts.

There are four robotic arms that transfer fluid to cuvettes at four different delivery stations on the MDA 180 (see Figure 1). Arm one

delivers sample plasmas (20), reference plasmas (22), and control plasmas (24). Arm two and three deliver various buffers (30) and activators (40) for various specific assays. Arm four delivers various reagents (45) that initiate the reaction to be monitored, usually at least one being used in every assay. The specimen barcodes are read at arm one. Once the sample is identified, the assays ordered for it are retrieved from either the instrument database or the laboratory information system (LIS). In addition, material availability must be verified (including loading a cuvette onto the cuvette track if required), assay instructions distributed throughout the system, and sample plasma aspirated and dispensed into one of the cuvette reaction wells (each cuvette has four reaction wells). Cuvettes in the track advance discrete increments at fixed 20-second intervals. Thus, everything that must happen to the cuvette at each arm must be completed in 20 seconds. Assay reagents are added, if necessary, by probes at arms two and three, and the last reagent is added by a probe at arm four. Optical measurements, which are used to calculate assay results, are begun after addition of reagent at arm four.

A common vehicle for reagent cross-contamination is the surface of the reagent probe which transfers reagents from their storage container to the reaction well. For the MDA 180, potential exists for cross-contamination at the sample probe and at all three reagent probes. However, many of these can be addressed by short probe-washing procedures that can be completed within the 20-second cycle in which reagent is delivered. For some reagents, cross-contamination issues are potentially more serious and require more extensive washing of the probe. In a continuous, fixed cycle, fixed delivery point system such as the MDA 180, this extended washing requires that a reaction well be skipped so that one cycle may be used for cleaning instead of reagent delivery. These skipped wells have three disadvantages associated with them: (1) use of cleaning fluid and cuvette wells increases cost, (2)

more waste is generated, and (3) use of skipped wells reduces throughput (number of tests completed per hour).

The present invention is directed to optimally reordering a sequence of assays so as to minimize the problems noted above. Any solution to these problems, however, would have to be developed while maintaining existing features of the automated random access analyzer. Any solution would need to be fast due to these time constraints; and be flexible to readily accommodate changes to the way in which assays are sequenced due to changes in assays, reagents, hardware, etc., that may occur over time.

SUMMARY OF THE INVENTION

Therefore, it is an object of the present invention to provide a method to minimize the additional time and cuvettes necessary for probe washing to prevent cross-contamination. More particularly, it is an object of the present invention to sequence assays in an optimal way to minimize wasted time and cuvette wells.

These and other objects are provided by a method, and an apparatus for performing the method, which comprises:

providing at least one sample to be tested;

identifying a plurality of assays to be run on the sample(s);

providing a knowledge base of cross-contamination issues and their penalties;

utilizing the knowledge base to search the state space for an optimal sequence for the plurality of assays; and

performing the plurality of said assays in the optimal sequence.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is an illustration of the four arms for delivering reagents to cuvette wells in an automated coagulation instrument;

Figure 2 is a flow chart of steps in the method of the present invention;

Figure 3 is an illustration of an example of a search strategy for optimally ordering three assays on a single sample before the next sample is processed; and

Figure 4 is an illustration of a flow chart for branch and bound assay sequencing.

DESCRIPTION OF PREFERRED EMBODIMENTS

In the present invention, any of a variety of different assays are scheduled to run on a sample prior to the next sample in an optimal sequence based on knowledge about cross-contamination issues related to all assays. If up to 12 assays can be ordered for a sample from a variety of 40 assays, there are 2.772×10^{18} possible sequences. In an automated random access analyzer such as the MDA 180, reaction vessels advance from one position to the next in discrete increments at fixed intervals. Everything that must happen to the reaction vessel must happen to a reaction vessel at each position must occur within the fixed increment of time. In order to facilitate a quick response to STAT samples, barcodes are often read at the last possible moment before processing begins. If the automated analyzer is connected to an LIS, the analyzer must wait for the LIS to respond with the assays ordered for that barcode. Once the assays ordered are known, materials must be verified, assay instructions distributed, and the first aliquot of sample aspirated from its container and dispensed to the reaction vessel. If this does not all occur within the fixed time interval, a reaction vessel is skipped, possibly wasting material and reducing throughput. Reducing the time interval to accommodate additional or slower processes also reduces throughput. Therefore, there is very little time available to exhaustively explore all assay sequences in order to determine the optimal one.

This invention is a method and an apparatus to optimize the sequence of assays such that the fixed time interval is minimized, the quantity of extra washing steps to prevent random access cross-contamination are minimized, and assay precision and accuracy are maximized. This method allows a knowledge base concerning the relationships associated with random access cross-contamination to be utilized in optimally ordering assays run on a sample. This knowledge base is utilized during a "branch-and-bound" approach searching the state space. The knowledge base is contained in "rules" and "facts".

Optimization Function

In optimization problems, there is some function of a set of parameters, $f(x_1, x_2 \ldots x_n)$, that is being either minimized or maximized. With the assay sequencing problem, the parameters are the assays ordered for a given sample and the assay(s) scheduled to run prior to them. The function that is to be minimized is the total random access penalty (TRAP) associated with these assays. There are different types of penalties associated with assay sequences. Three examples are: (1) one (or more) wells must be skipped after an assay is run to allow for extensive washing to prevent cross-contamination to another assay run afterwards; (2) running assays in a particular sequence is acceptable, but minor cross-contamination issues may exist and alternative sequences would be preferable; and (3) not all assays use the probe that needs extra cleaning and some assays could be run concurrently with extensive washing, thus eliminating a skipped well.

Representation of Knowledge

Knowledge of conditions that must be met for penalties to be assessed to assays in a specific sequence has been encapsulated in facts and rules. Facts define characteristics of the following type:

"Assay 'X' is in a group 'Y' ". Each fact begins with '[IS-A]'. An example is

[IS-A]PT Screening,HEP or Not Arm 3

where the assay is "PT Screening" and the group is "HEP or Not Arm 3". This characteristic means the prothrombin time (PT) screening assay is identified as a member of a group that includes both heparin assays and assays that do not use the probe at arm 3.

Rules have a left hand side (LHS) and a right hand side (RHS). The LHS describes the pattern of assay types using the groups defined in the right hand side of the characteristics; the RHS defines the penalties associated with that pattern. Each rule starts with [RULE]c, where 'c' is the length of the pattern. The logical {NOT} is available to specify all assays that are 'not' of some type that follows {NOT}. Variable-length placeholders, 'n', may also be used in the internal portions (any place except the first or last position in a pattern) of the LHS to represent 0 to ∞ assays with any type of assay. An example of a rule is

[RULE]2,HEP,{NOT}HEP or Not Arm 3,0.1

which means if any assay that is not in the group 'HEP or Not Arm 3' follows behind a HEP group assay, then a penalty of 0.1 is applied to the HEP assay. The purpose of this particular rule is to make sure that if possible, either a heparin (anti-Xa) assay or one that does not use probe three is placed after a heparin (anti-Xa) assay so that either no extensive washing is required (heparin) or a well does not have to be skipped to allow for extensive washing (assays that do not use arm 3) of the probe at arm three. The right hand side of the rule can be truncated at the last non-zero penalty, and all others past the last one will then be assumed

to be zero. The corresponding value in the RHS will be applied to all assays represented by 'n'.

Each whole penalty (1.0) corresponds to one extended washing (EW). Partial penalties less than 1 are used in the optimization, but stripped from the resulting best sequence at the end of the process before a resulting sequence is returned. Partial penalties can be used to express situations which do not require extensive washing, but are still not optimal. These can be expressed in levels of importance as well.

State Space Search Strategy

Once the rules are established, a method is required to find the optimal sequence (goal state) of an assay order list for a specimen. State space describes all of the partial paths between the initial state(s) (or root(s)) and ending states. Each state is represented by a node and these nodes are connected by directed arcs which describe how to get from one state to the next. If a directed arc from N_i connects to N_j, N_i is a parent of N_j and N_j is a child of N_i. An ordered sequence of nodes $(N_1, N_2, N_3 \ldots N_n)$ where each N_i, N_{i+1} in the sequence represents an arc (N_i, N_{i+1}) is called a path. At the end of each path is a leaf node, which has no children. In the assay sequencing problem, the initial state (or root node) is the list of assays already scheduled. Each arc represents an assay in a particular sequence. Each node represents some partial sequence of assays.

If the maximum of 12 assays are ordered, and there are 40 possible assays that can be ordered, the possible sequences are 40!/28! or 2.676×10^{18}. The total possible sequences include the sequences from 1 assay ordered to 12 assays

ordered, or 40!/28! +40!/29! +...40!/39! = $= 2.772 \times 10^{18}$.

If 12 assays are ordered, there are 12! or 479,001,600 possible sequences to explore just for that specific set of assays. An exhaustive

search of these many combinations would be inefficient on any system and prohibitive on the MDA 180 system given its time limitations. Thus the method employed must minimize both the storage space and the number of possible paths examined.

The particular method employed to efficiently search the state space for the optimal sequence problem is described by the following steps:

1. The root node is the first one expanded (called the E-node). Expanding means that all of its possible children are identified.
2. The first child of the current node is then selected as the next E-node. Again, all possible children are identified for that node.
3. Step 2 is repeated until a leaf node is reached. This is considered a depth-first approach.
4. Once the leaf node is reached, a cost function, or bounding function is computed for the path. This value becomes the "bound" and the path becomes the current "best" path.
5. Backtracking from the leaf node to the last node created, an unexplored child node and all of its ancestors become a partial "test" path.
6. The rules are applied to this path, and the cost function is computed.
7. If the test path cost is not less than the best path cost, then this newest E-node is bound, and none of its descendants are examined. If it is less, then all children of this new E-node are identified, and the last child becomes the new E-node.
8. If the test path reaches a leaf node and has less cost than the best path, the best path is replaced by the test path, a new bound is established based on the test path cost, and

the old best node at the same level as the first E-node of the test path is bound.

Steps 5 through 8 are repeated until one of two goal conditions are reached: (1) there are no children left to examine that are unbound, or (2) the cost is zero.

Example

An example of this search strategy as applied to the assay sequencing problem is depicted in Figure 3. In this example, there are three assays ordered, activated partial thromboplastin time (APTT), prothrombin time (PT), and heparin (HEP). Assume that heparin is the last assay scheduled to run before this specimen's assays. The characteristics are:

[IS-A]PT Screening,HEP or Not Arm 3
[IS-A]Heparin (Anti-Xa),HEP or Not Arm 3
[IS-A]Heparin (Anti-Xa), HEP.

Assume the only rules are :

[RULE]2,HEP,{NOT}HEP,1
[RULE]2,HEP,{NOT}HEP or Not Arm 3,0.1
[RULE]2,{NOT}HEP,HEP,0.05.

The intent of the first rule is to place all heparin assays together since extensive washing is only necessary at the end of a series of these assays. The second rule has been described earlier. The third rule exists to prevent heparin assays from being placed at the end of a sequence to avoid the first rule if the heparin assay can be run and the probe at arm 3 washed without skipping a well.

The first step is to create the initial best path HEP-APTT-PT-HEP (nodes: root-2-3-4). All three rules fire once, yielding a TRAP of 1.15, the initial bound value. In the next step, rules are applied to HEP-APTT-HEP. The TRAP for this is 1.15 when all three rules fire, so node 5 is bound. Next, the rule is applied to path HEP-HEP (TRAP = 0.0); then HEP-HEP-PT (TRAP = 1.0); then HEP-HEP-PT-APTT (TRAP = 1.0). The TRAP for HEP-HEP-PT-APTT is less than the bound, so this becomes the new best node and node 2 is bound. Next, path HEP-HEP-APTT yields a TRAP of 1.1, and node 9 is bound. Path HEP-PT has a TRAP of 1.0 which is no better than the current bound value , and node 10 is bound. There are no more unbound nodes to explore, therefore goal 2 has been met and the search is terminated. In this example, the use of assay sequencing to determine the optimal path of HEP-HEP-PT-APTT potentially eliminates two extensive washings and two associated skipped wells.

Further Examples

A list of characteristics and rules is shown in the following Table 1:

Table 1.

Characteristics:	
[IS-A]AT III,AT-III	[IS-A]Factor VII,AT-III or Not Arm 3
[IS-A]Plasminogen,PLG	[IS-A]P&P 1,AT-III or Not Arm 3
[IS-A]Heparin (anti-Xa),HEP	[IS-A]P&P 2,AT-III or Not Arm 3
[IS-A]LMW Heparin,HEP	[IS-A]TT,AT-III or Not Arm 3
[IS-A]Heparin (anti-Xa),HEP or Not Arm 3	[IS-A]Fibrinogen,AT-III or Not Arm 3
[IS-A]LMW Heparin,HEP or Not Arm 3	[IS-A]Lupus Screen,AT-III or Not Arm 3
[IS-A]PT Screening,HEP or Not Arm 3	[IS-A]Lupus Check,AT-III or Not Arm 3
[IS-A]Factor VII,HEP or Not Arm 3	[IS-A]PT INR,AT-III or Not Arm 3
[IS-A]P&P 1,HEP or Not Arm 3	[IS-A]PT Mix,AT-III or Not Arm 3
[IS-A]P&P 2,HEP or Not Arm 3	[IS-A]Factor X PT,AT-III or Not Arm 3
[IS-A]TT,HEP or Not Arm 3	[IS-A]Factor II,AT-III or Not Arm 3
[IS-A]Fibrinogen,HEP or Not Arm 3	[IS-A]PT A,AT-III or Not Arm 3
[IS-A]Lupus Screen,HEP or Not Arm 3	[IS-A]PT B,AT-III or Not Arm 3
[IS-A]Lupus Check,HEP or Not Arm 3	[IS-A]Fibrinogen (II),AT-III or Not Arm 3
[IS-A]PT INR,HEP or Not Arm 3	[IS-A]TT A,AT-III or Not Arm 3
[IS-A]PT Mix,HEP or Not Arm 3	[IS-A]PT Factor,AT-III or Not Arm 3
[IS-A]Factor X PT,HEP or Not Arm 3	[IS-A]PT Quick Pct,AT-III or Not Arm 3
[IS-A]Factor II,HEP or Not Arm 3	[IS-A]Plasminogen,PLG or Not Arm 3
[IS-A]PT A,HEP or Not Arm 3	[IS-A]PT Screening,PLG or Not Arm 3
[IS-A]PT B,HEP or Not Arm 3	[IS-A]Factor VII,PLG or Not Arm 3
[IS-A]Fibrinogen (II),HEP or Not Arm 3	[IS-A]P&P 1,PLG or Not Arm 3
[IS-A]TT A,HEP or Not Arm 3	[IS-A]PT B,PLG or Not Arm 3
[IS-A]PT Factor,HEP or Not Arm 3	[IS-A]Fibrinogen (II),PLG or Not Arm 3
[IS-A]PT Quick Pct,HEP or Not Arm 3	[IS-A]TT A,PLG or Not Arm 3
[IS-A]AT III,AT-III or Not Arm 3	[IS-A]PT Factor,PLG or Not Arm 3
[IS-A]PT Screening,AT-III or Not Arm 3	[IS-A]PT Quick Pct,PLG or Not Arm 3

Rules:
[RULE]2,HEP,{NOT}HEP or Not Arm 3,0.1
[RULE]2,HEP,{NOT}HEP,1
[RULE]2,{NOT}HEP,HEP,0.05
[RULE]2,AT-III,{NOT}AT-III or Not Arm 3,0.1
[RULE]2,AT-III,{NOT}AT-III,1
[RULE]2,{NOT}AT-III,AT-III,0.05
[RULE]2,PLG,{NOT}PLG or Not Arm 3,0.1
[RULE]2,PLG,{NOT}PLG,1
[RULE]2,{NOT}PLG,PLG,0.05

Based on the characteristics and rules of Table 1, assays would be resequenced as shown in the following Table 2:

Table 2.

	Order	Unoptimized Sequence	Optimized Sequence
1	AT-III (P)	AT-III (P)	AT-III (P)
	APTT Screening	(SW)	AT-III
	AT-III	APTT Screening	PT Screening
	Factor VIII	AT-III	Factor VIII
	PT Screening	(SW)	APTT Screening
		Factor VIII	
		PT Screening	
2	Heparin (anti-Xa)(P)	Heparin (anti-Xa) (P)	Heparin (anti-Xa)(P)
	PLG	(SW)	(SW)
	APTT	Plasminogen	Plasminogen
	Fibrinogen (II)	(SW)	APTT
		APTT	Fibrinogen (II)
		Fibrinogen (II)	
3	Heparin (anti-Xa)(P)	Heparin (anti-Xa)(P)	Heparin (anti-Xa)(P)
	APTT Screening	(SW)	Heparin (anti-Xa)
	Heparin (anti-Xa)	APTT	TT
	Plasminogen	Heparin	Antithrombin-III
	AT-III	(SW)	PT Screening
	PT Screening	Plasminogen	APTT Screening
	TT	(SW)	Plasminogen
		AT-III	
		(SW)	
		PT Screening	
		TT	

NOTES: 'P' Represents previously run assay.

'SW' Represents skipped well.

Method Description

The MDA 180 is built using a multi-tasking operating system. When a barcode is read, the instrument database is searched to see if it exists. If the barcode is not found in the instrument database, the LIS is queried to see if there are any pending assays for that particular barcode. Once the pending assays are identified, materials such as reagents and cuvette wells are checked to see if they are available. If materials are available for an assay, they are then committed to that assay. Otherwise, that assay is not placed in the queue. Once all the assays for a barcode are in the queue, they are sent to be sequenced. Once the optimal sequence is returned, the assays are then scheduled and then physically performed.

In the general method of the invention as illustrated in Figure 2, a sample is provided (60) for testing. A plurality of assays (65) are identified which are to be run on the sample. A knowledge base of cross-contamination issues (and their penalties) is provided (70). Then, using the knowledge base, the state space is searched (75) for an optimal sequence (80) for the assays. Finally, the assays are performed (85) in the thus determined optical sequence. This method can also be performed whereby more than one sample is provided, and a plurality of assays are identified and performed in an optimal sequence on the plurality of samples.

Figure 4 depicts a flow chart of an assay sequencing "branch and bound" method. The first major procedure is initialization (100). This occurs when the assay sequencing task is started and includes allocation of memory, and initialization of data; reading of assay, characteristic, and rule definitions. Text-based initialization files contain three lists: a list of assays and their associated integer codes, a list of characteristics, and a list of rules. The text strings in the characteristics and rules are converted via a table to integers for quicker comparisons during the optimization process. Once initialization is complete, the task waits for

a message identifying two arrays: the assays ordered for the current specimen and the last assay scheduled prior to the current specimen. Once this message is received, the test and best node arrays are initialized and then the optimization process begins.

The first step in the optimization process is to determine the initial best path. It includes loading the best path array (102) with the assays ordered "as-is" (104), identifying all unexplored children of each node in the best path (106), and applying the rules (108) to identify the current best path TRAP.

Once an initial best path is established, the iterative process of looking for a better alternative may begin. The first step in this iterative process is to check to see if any of the goal conditions have been met with the current best path. The two goals are: (1) TRAP = 0 (120) and (2) there are no unexplored children (122). If either of these goals are met, the optimization process stops and the new order is returned (124) by the task with EW inserted in the new order as necessary. If neither of the goal conditions are met, the lowest node in the tree with an unexplored child is identified (126). This unexplored child with all of its ancestors are copied into the test node (128). Rules are applied (140) and the test TRAP is determined. If the test TRAP is more than the best TRAP (142), the last node in the test path is removed (144) and the process of looking for the lowest unexplored child (146) in the test path begins. If the test TRAP is less than the best TRAP and there are no children of the last node (150) , then the current best path is replaced with the current test path (152). Otherwise, an unexplored child is added to the end of the test path and the process of applying the rules is repeated. In the event that the time available for searching has expired, the process is halted and the best path found to that point is returned.

The calculations in the present invention are preferably implemented by software. The computer for controlling the automated

apparatus can also be for the present invention. The computer can be based on one or more Intel® 386 or higher chips, for example, and any of a number of operating systems such as QNX.

In a further embodiment of the invention described above, this method could also be used to optimize assays for more than one sample at the same time in a hybrid random access - batch mode, where the analyzer can run any of a plurality of assays on any of a plurality of samples within a given batch of samples.

The method of the present invention, developed to optimize the order of coagulation assays performed on a sample, provides the ability to increase throughput, increase precision and accuracy of results, and reduce the use of instrument resources with no additional costs associated with consumables or equipment. Given the assay(s) already scheduled, the assays ordered for the current sample, rules expressing assay sequence patterns and their associated penalties, and facts describing assays, the invention can determine the optimal sequence of the assays ordered and the placement of any extensive washing.

While there have been described what are presently believed to be the preferred embodiment of the invention, it will be apparent to one skilled in the art that numerous changes can be made to the parameters set forth in the foregoing embodiments without departing from the invention as described herein as defined in the appended claims.

WE CLAIM:

1. A method of ordering assays on an analyzer with random access to a plurality of assays in such a way as to minimize the problems associated with cross-contamination, comprising:

a) providing a sample to be tested;

b) identifying a plurality of assays to be run on said sample;

c) providing a knowledge base of cross-contamination issues and their penalties;

d) utilizing said knowledge base to search the state space for an optimal sequence for the plurality of assays; and

e) performing said plurality of said assays in said optimal sequence.

2. A method according to claim 1, wherein assays scheduled for a sample previous to said sample are known and utilized in the state space search.

3. A method according to claim 1, wherein said state space search is based on a branch and bound method.

4. A method according to claim 1, wherein the knowledge base of cross-contamination issues is represented by a set of characteristics which describe or group assays, and a set of rules which define patterns of assays and their associated cross-contamination penalties.

5. A method according to claim 1, wherein said knowledge base of said cross-contamination issues include at least one of: (1) additional time is required for washing a reagent delivery probe, (2) precision of subsequent assay affected, (3) additional material is required for probe washing, and (4) more expensive or less desirable material is required for washing.

6. A method according to claim 4, wherein said search is based on an optimization function which is the total cross-

contamination penalties assessed due to particular sequences encountered in the search.

7. A method according to claim 1 wherein said plurality of assays are coagulation assays.

8. A method according to claim 7 wherein the coagulation assays include: prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen, heparin anti-Xa, plasminogen, protein C, and antithrombin III.

9. A method according to claim 1, wherein said performing of said plurality of assays in said optimal sequence includes delivering the sample to a reaction well and delivery reagents to said reaction well to initiate a reaction.

10. A method of ordering assays on an analyzer with random access to a plurality of assays in such a way as to minimize the problems associated with cross-contamination, comprising:

a) providing a plurality of samples to be tested;

b) identifying a plurality of assays to be run on the samples;

c) providing a knowledge base of cross-contamination issues and their penalties;

d) utilizing said knowledge base to search the state space for an optimal sequence for the plurality of assays; and

e) performing said plurality of said assays in said optimal sequence.

11. A method according to claim 10, wherein assays scheduled for a sample previous to said plurality of samples are known and utilized in the state space search.

12. A method according to claim 10, wherein said state space search is based on a branch and bound method.

13. A method according to claim 10, wherein the knowledge base of cross-contamination issues is represented by a set of characteristics which describe or group assays, and a set of rules

which define patterns of assays and their associated cross-contamination penalties.

14. A method according to claim 10, wherein said knowledge base of said cross-contamination issues include at least one of: (1) additional time is required for washing a reagent delivery probe, (2) precision of subsequent assay affected, (3) additional material is required for probe washing, and (4) more expensive or less desirable material is required for washing.

15. A method according to claim 13, wherein said search is based on an optimization function which is the total cross-contamination penalties assessed due to particular sequences encountered in the search.

16. A method according to claim 10 wherein said plurality of assays are coagulation assays.

17. A method according to claim 16 wherein the coagulation assays include: prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen, heparin anti-Xa, plasminogen, protein C, and antithrombin III.

18. A method according to claim 10, wherein said performing of said plurality of assays in said optimal sequence includes delivering the sample to a reaction well and delivery reagents to said reaction well to initiate a reaction.

19. An apparatus for ordering assays on an analyzer with random access to a plurality of assays in such a way as to minimize the problems associated with cross-contamination, comprising:

a) means for providing at least one sample to be tested;

b) means for identifying a plurality of assays to be run on said at least one sample;

c) means for providing a knowledge base of cross-contamination issues and their penalties;

d) means for utilizing said knowledge base to search the state space for an optimal sequence for the plurality of assays; and

e) means for performing said plurality of said assays in said optimal sequence.

20. An apparatus according to claim 19, wherein assays scheduled for a sample previous to said at least one sample are known and utilized in the state space search.

21. An apparatus for according to claim 19, wherein said state space search is based on a branch and bound method.

22. An apparatus according to claim 19, wherein the knowledge base of cross-contamination issues is represented by a set of characteristics which describe or group assays, and a set of rules which define patterns of assays and their associated cross-contamination penalties.

23. An apparatus according to claim 19, wherein said knowledge base of said cross-contamination issues includes at least one of: (1) additional time is required for washing a reagent delivery probe, (2) precision of subsequent assay affected, (3) additional material is required for probe washing, and (4) more expensive or less desirable material is required for washing.

24. An apparatus according to claim 22, wherein said search is based on an optimization function which is the total cross-contamination penalties assessed due to particular sequences encountered in the search.

25. An apparatus according to claim 19 wherein said plurality of assays are coagulation assays.

26. An apparatus according to claim 25 wherein the coagulation assays include: prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen, heparin anti-Xa, plasminogen, protein C, and antithrombin III.

27. An apparatus according to claim 19, wherein said means for performing said plurality of assays in said optimal sequence includes means for delivering the sample to a reaction well and means for delivering reagents to said reaction well to initiate a reaction.

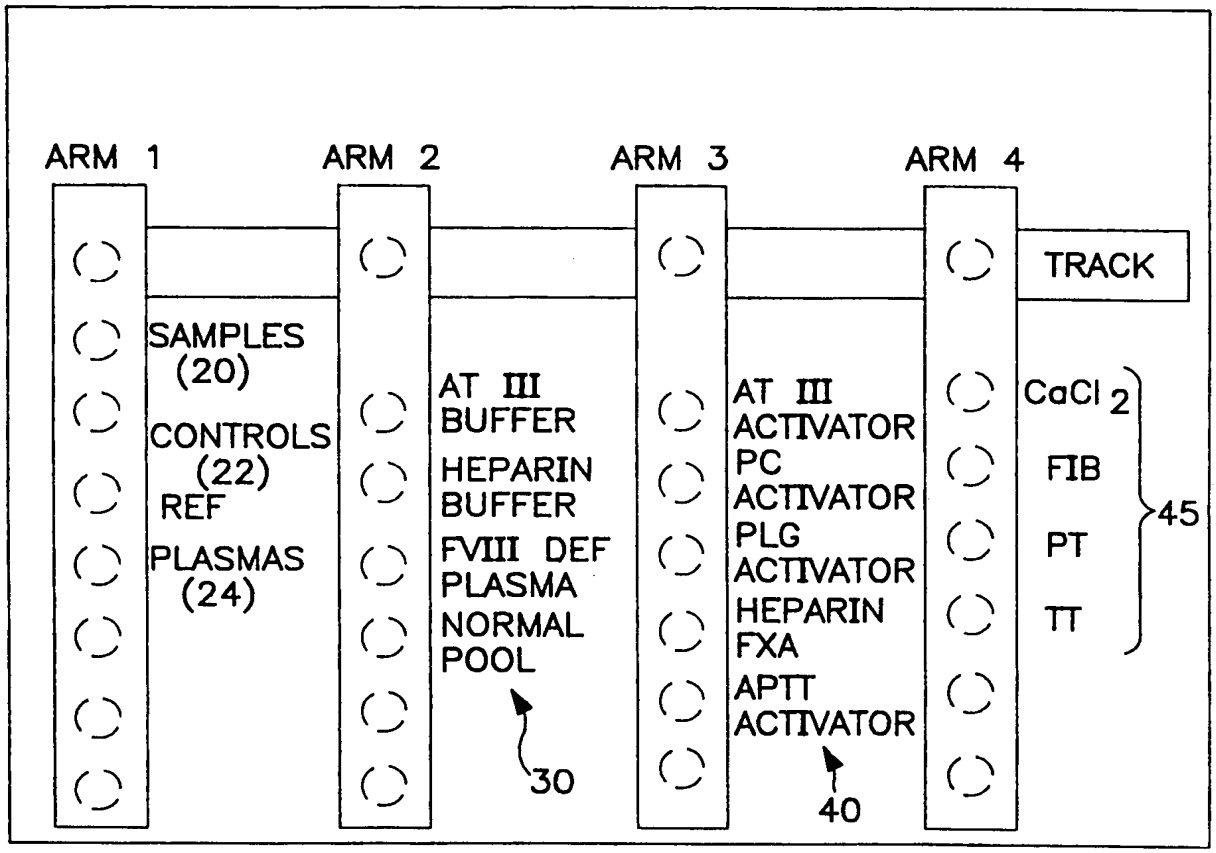

FIG. 1

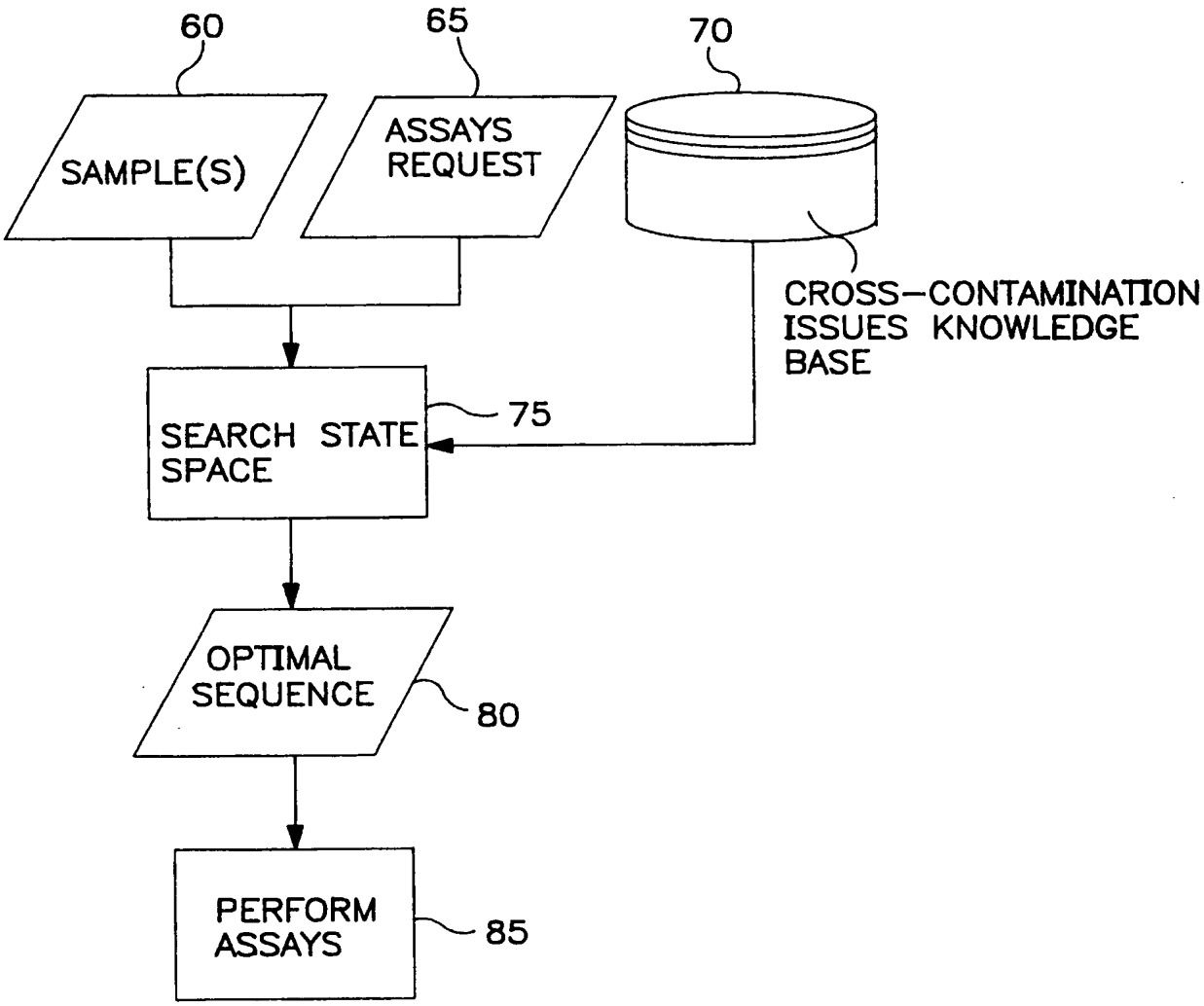

FIG 2

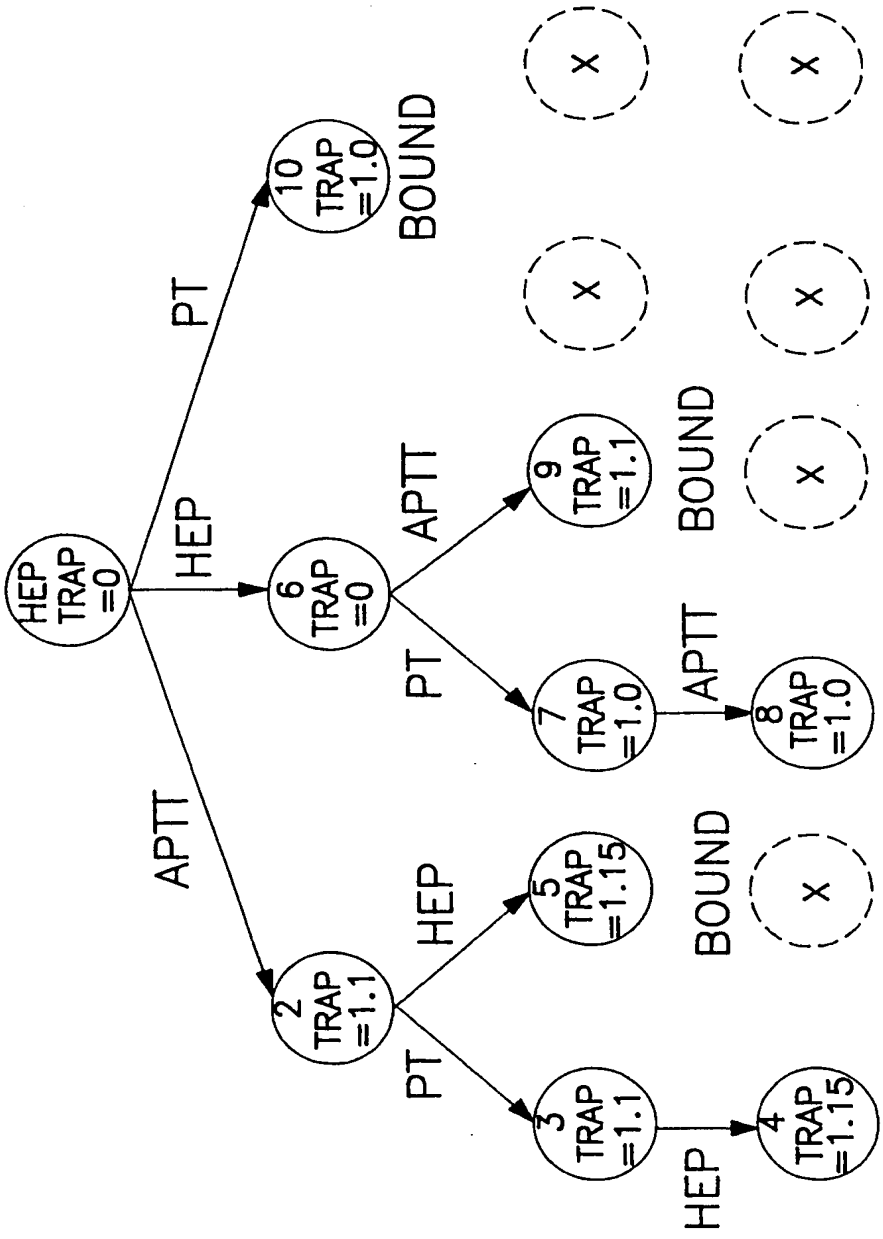

FIG .3

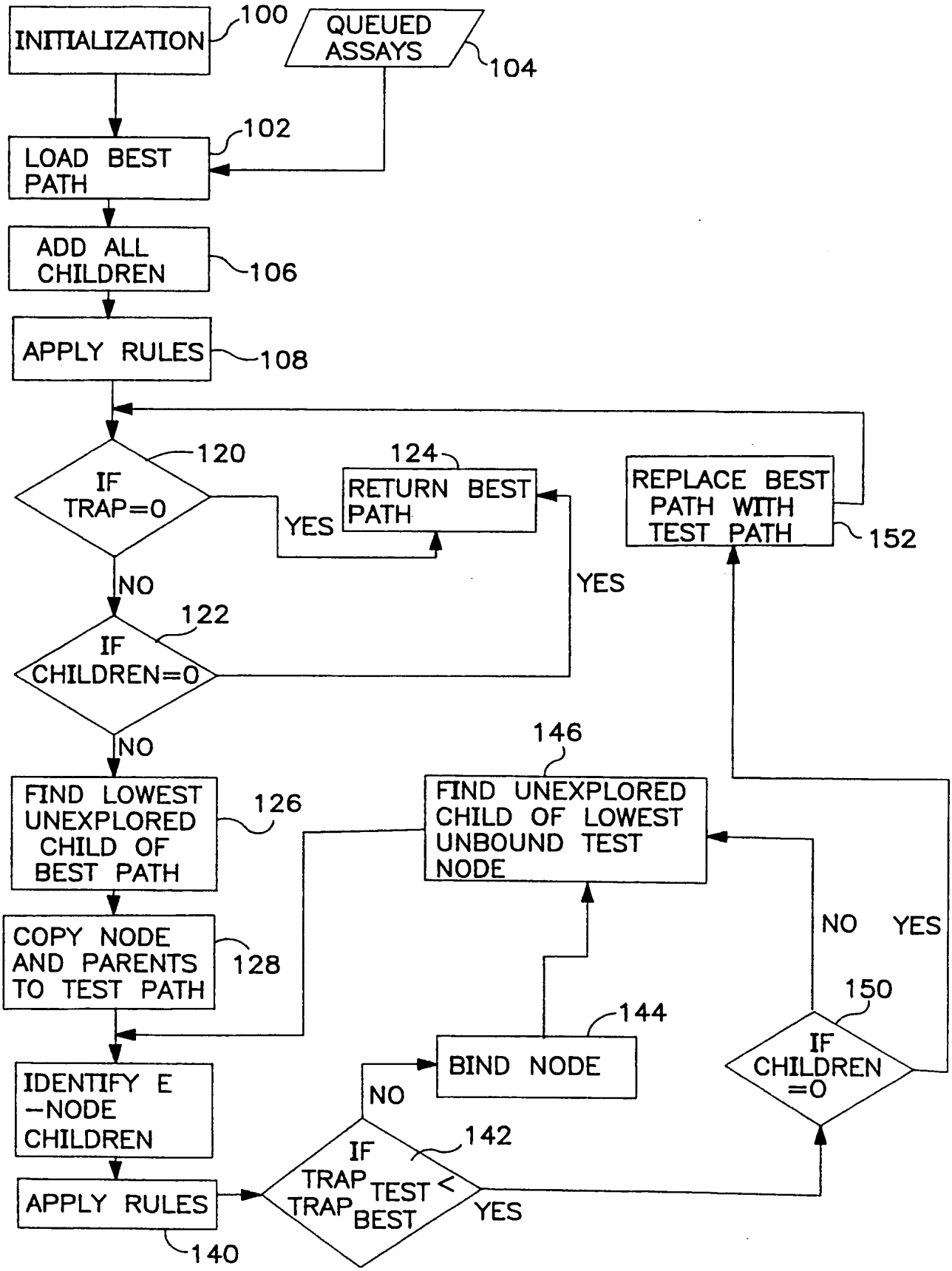

FIG. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/07246

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :G01N 1/36, 35/00
US CL :422/63, 67, 73; 436/43, 47, 49, 50
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 422/63, 67, 73; 436/43, 47, 49, 50

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,971,913 A (MANABE et al.) 20 November 1990, the abstract, columns 4-7.	1-6, 9-15, 18-24 and 27
Y	US 4,695,430 A (COVILLE et al.) 22 September 1987, Background of the Invention section.	7, 8, 16, 17, 25 and 26
A	US 4,908,320 A (ZAKOWSKI et al.) 13 March 1990, whole document.	1-27
A	US 5,100,622 A (MIMURA et al.) 31 March 1992, whole document.	1-27

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 JUNE 1998	20 JUL 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer LONG V. LE Telephone No. (703) 308-0651

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